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K Kannan
Assistant Professor, Veterinary Clinical Complex, Veterinary College and Research Institute, Tamil Nadu Veterinary and Animal Sciences University, Orathanadu, Thanjavur District, Tamil Nadu, India

Sakthi Karthikeyan
M.V.Sc., Scholar, Department of Veterinary Pharmacology and Toxicology, C.V. A.Sc, GBPUA&T, Pantnagar, Uttarkand, India

AH Ahmad
Professor and Head, Department of Veterinary Pharmacology and Toxicology, C.V.A.Sc, GBPUA&T, Pantnagar, Uttarkand, India

HK Pandey
Ph.D., Scholar, Department of Veterinary Pharmacology and Toxicology, C.V.A.Sc, GBPUA&T, Pantnagar, Uttarkand, India

A Elamaran
Assistant Professor, Department of Veterinary Pharmacology and Toxicology, Veterinary College and Research Institute, Tamil Nadu Veterinary and Animal Sciences University, Orathanadu, Thanjavur District, Tamil Nadu, India

Corresponding Author:
A Elamaran
Assistant Professor, Department of Veterinary Pharmacology and Toxicology, Veterinary College and Research Institute, Tamil Nadu Veterinary and Animal Sciences University, Orathanadu, Thanjavur District, Tamil Nadu, India

Acute toxicity study of aqueous extract of *Panax ginseng* root in rats

K Kannan, Sakthi Karthikeyan, AH Ahmad, HK Pandey and A Elamaran

Abstract
A study was conducted in wistar rats to know the acute toxic effect of aqueous extract of *Panax ginseng* root. It was given orally @ 1g/kg, 2g/kg and 3g/kg. b.wt., for two weeks period as a single dose. No apparent clinical manifestations and gross lesions in body organs of rats were recorded. A significant decrease in Hb was observed in rats given aqueous extract @ 2 and 3g/kg as compared to control rats. The total serum protein value in rats administered with aqueous extract @ 3g/kg increased significantly whereas, serum albumin, serum globulin and A:G values showed no significant difference. Serum glucose was significantly increased in aqueous extract @ 3g/kg. Rats treated with aqueous extract @ 2 and 3g/kg showed significant difference in serum creatinine, cholesterol, AST and ALT as compared to control. Rats of all groups showed no significant difference, but rats administered with aqueous extract @ 3g/kg showed significant decrease in level of RBC LPO in comparison to the untreated control. Significant increase was observed in liver LPO level of rats treated with aqueous extract @ 3g/kg as compared to control.

Keywords: *Panax ginseng* root, acute toxicity, haematology, biochemical, rats

Introduction
Ginseng, the root of perennial herbs of *Panax ginseng* contains a series of tetracyclic triterpenoid, saponins ginsenosides as active ingredients. It is considered a tonic or adaptogenic that enhances physical performance (including sexual), promotes vitality and increases resistance to stress and ageing [1]. The adaptogenic properties of ginseng are believed to be due to its effects on hypothalamic-pituitary-adrenal axis, resulting in elevated plasma corticotropin and corticosteroids levels. Ginseng appears to be safe, when used appropriately [2]. With regard to acute toxicity study of aqueous extract of *Panax ginseng* in rats, there is no much data available. Therefore, the present study is conducted to know the acute toxicity of aqueous extract of *Panax ginseng* in rats.

Materials and Methods
Experimental animals
Albino rats (Wistar) of 2 to 2.5 months of age, weighing between 180 to 210 gm, were procured from Laboratory Animal Resource Centre, IVRI, Izatnagar. The animals were kept in plastic cages and were acclimatized for two weeks in the experimental laboratory animal shed of the Department of Pharmacology, College of Veterinary and Animal Sciences, Pantnagar, under standard managemental conditions. Standard rat feed and water were provided *ad libitum* throughout the experimental period. The experimental protocol was approved by the Institutional Animal Ethic Committee.

Plant material and preparation of extract
The plant materials were procured from JKH Herbs and Spices, Navimumbai and identified by the department of Plant Physiology, Pantnagar. The dried roots of *Panax ginseng* were powdered. The powder was soaked in distilled water for 24 hours with continuous stirring at 40ºC. The mixture was filtered through muslin cloth and whatman filter paper no.1, the solvent was concentrated in a rotatory vacuum evaporator at 40-50 ºC. The final extract was produced after drying the filtrate in incubator with fan (40ºC) and lyophilized. The percentage yield of extract was 11.1%.

Experimental design
Rats of 2 to 2.5 months of age were randomly divided into four groups (group-I(control), II,III,IV(treatment group) with 3 rats in each group. Experiment was designed as per OECD guidelines and 1/5th dose (1g.kg^{-1} b.w.) of oral LD_{50} of *Panax ginseng* (>5 g.kg^{-1}) [3]

was administered in the first group as single oral dose in the form of gastric gavage using a plastic tube fitted to the tip of a plastic syringe. The dose was increased to 2 and 3g.kg^{-1} b.w. in the subsequent groups for study of acute toxicity. Rats were constantly observed for consecutive 14 days for appearance of specific clinical signs as well as mortality due to plant toxicity. On 15th day, all the rats were sacrificed. The viscera and internal organs were examined for gross lesions, samples of blood and liver samples were collected to evaluate haematological, biochemical and antioxidative parameters. After completion of experiment, all rats were sacrificed and buried scientifically. Blood samples collected were subjected for serum AST, ALT, ALP, Glucose, Urea, Creatinine, Cholesterol, Total proteins and Albumin estimation by using Diagnostic Kits procured from Span Diagnostics Ltd., Surat. Haematological parameters were estimated in blood as per the method given [4]. Comparisons among treated and untreated groups were made employing student 't' test. Statistically significant difference was considered at 5 percent level.

Results and Discussion

The results of the study are enlisted in Table 1. Administration of aqueous extracts (1, 2 and 3g/kg b.wt) of *Panax ginseng* as a single dose to groups II, III and IV, respectively, did not produce any apparent toxic signs in rats. Our findings are in accordance with the findings [5], where they recorded no toxic effect in beagle dogs fed with 0, 1.5, 5 or 15 mg of ginseng extract per kg of body weight per day for 90 days. In the present study, significant increase (P<0.05) in relative weight of liver was observed in rats treated with *Panax ginseng* (3g/kg.b.wt) (Table.1). This increase in liver weight may be attributed to proliferation of smooth endoplasmic reticulum. Such alteration of the hepatic system may directly or indirectly influence the function of lymphatic system. No significant change was observed in value of PCV as compared to control in groups II, III, IV however, significant decrease in the value of hemoglobin was observed at higher dose levels (Table.1). Haemolysis and shrinkage in RBC might be the reason for decline in haemoglobin in treated rats. No significant change was observed in protein profile of treated rats in all the groups except for significant (P<0.05) increase in total protein in rats of group IV (Table.1). This might be attributed to enhanced release of proteins from liver into blood circulation in rats. A significant (P<0.05) increase in level of glucose was found to occur in rats of group IV (Table.1). Acute hyperglycemia was reported to cause oxidative stress by various mechanisms in human beings [6] and rats [7]. A significant (P<0.05) increase in serum cholesterol level was recorded in groups III and IV (Table.1). Liver is the major site of cholesterol, bile acid and phospholipids synthesis and metabolism. Hepatic cholesterol homeostasis is maintained by equilibrium between the activities of hydroxyl methyl glutaryl CoA (HMG-CoA) reductase and that of acyl CoA, cholesterol acyl transferase [8]. Thus, alteration in cholesterol level might have been due to effect on metabolism of cholesterol in this study.The serum concentrations of creatinine in groups III and IV were significantly higher (P<0.05) as compared to control group (Table.1). Higher level of creatinine is suggestive of nephrotoxic effect [9]. A significant increase in the activity of serum AST in treated groups (Table.1) might be due to hepatic damage caused by *Panax ginseng* in this study. The rise in serum levels of ALT and AST activity has been attributed to the loss of structural integrity of hepatocytes as these enzymes are located in the cytoplasm and are released into circulation after cellular damage [10]. There was significant reduction in lipid peroxidation (LPO) RBC status in group IV as compared to control (Table .1) which suggested that *Panax ginseng* did not produce oxidative stress in erythrocytes of *Panax ginseng* treated rats. The reduction in LPO in RBCs in the present study evidenced that the extract administration at higher doses resulted in the decline in production of malondialdehyde (MDA). No significant changes were observed in GSH profile of RBC tested. A significant increase was observed in liver LPO profile in rats of group IV, whereas in all groups non-significant difference in liver GSH level (Table.1) was observed which suggested that *Panax ginseng* promoted the synthesis of oxidative radicals in liver of *Panax ginseng* treated rats [10]. Thus it is essential to obtain information on the active ingredients / bioactive compounds from these plants their relative contribution to the effects of the extract (including for example, synergic or antagonistic effects) and the toxicological profile of the extract and its constituents [11].

Table 1: Acute toxicity study of aqueous extract of *Panax ginseng* root in rats

S. No.	Groups	Treatment			
	Parameters	**Control**	**PRA$_{1000}$**	**PRA$_{2000}$**	**PRA$_{3000}$**
1.	Clinical Observations	NIL	NIL	NIL	Depression, sluggishness and loss of appetite for first few days
2.a	**a. Body weight**				
1	1.0 day	183.33±1.67	191.67±7.26	186.67±14.53	205.00±10.41
2	2.7th day	185.00±2.89	195.00±7.64	190.67±16.75	208.33±10.14
3	3.14th day	183.67±2.73	186.83±6.34	185.17±18.48	206.67±11.26
B	**b. Organ weight**				
1	Relative liver weight	2.90±0.07	3.73±0.21	2.80±0.20	3.73±0.25 [a]
2	Relative kidney weight	0.82±0.01	0.71±0.08	0.72±0.05	0.87±0.05
3	Relative brain weight	0.73±0.09	0.79±0.02	0.83±0.08	0.64±0.06
3.	**Haematology**				
1	Haemoglobin (g/dl)	12.67±0.18	12.47±0.18	12.00±0.12	11.67±0.18[a]
2	PCV (%)	45.67±1.86	44.67±1.86	47.33±1.20	44.00±1.53
4.	**Serum Biochemical profile**				
i	Total Protein (g/dl)	7.32±0.07	7.35±0.08	7.37±0.03	7.77±0.11[a]
ii	Albumin (g/dl)	4.16±0.05	4.11±0.09	4.19±0.01	4.24±0.09
iii	Globulin (g/dl)	3.16±0.04	3.24±0.16	3.18±0.04	3.53±0.13
iv	A: G ratio	1.32±0.02	1.28±0.09	1.32±0.02	1.20±0.05
v	Glucose (mg/dl)	95.44±1.25	95.08±5.10	104.94±2.96	110.77±4.63[a]
vi	Cholesterol (mg/dl)	49.93±0.91	51.83±0.78	57.96±0.96[a]	59.37±0.56[a]

vii	Creatinine (mg/dl)	0.66±0.04	0.75±0.08	0.94±0.01[a]	0.98±0.02[a]
5.	**Serum Enzymic profile**				
i	AST (IU/L)	48.28±0.66	63.05±0.09[a]	63.29±0.46[a]	65.45±0.49[a]
ii	ALT (IU/L)	32.38±1.03	35.40±0.78	36.77±0.53[a]	39.34±0.49[a]
6.	**Antioxidative parameters**				
a	a.RBC	15.92±1.06	14.24±0.38	14.69±0.86	12.39±0.49[a]
i	.LPO(nMDA/ml)	0.85±0.09	0.83±0.08	0.93±0.03	0.80±0.14
ii	GSH(nMDA/ml)				
b	b.Liver				
i	LPO(nMDA/gm)	28.61±2.61	29.78±2.26	29.22±1.98	36.03±2.30[a]
ii	GSH(nMDA/gm)	2.92±0.16	2.82±0.17	2.92±0.21	3.04±0.22

Values in table are Mean ± S.E. (n = 3)
a = Significant difference (P<0.05) as compared to control group
PRA- Aqueous extract of *Panax ginseng* root
(PRA_{1000} –group II, PRA_{2000} –group III, PRA_{3000}–group IV)

Conclusion

It could be concluded from acute oral toxicity study of *Panax ginseng* in rats that it produces mild haemotoxic and moderate hepatotoxic effect at the dose level as high as $2g.kg^{-1}$ b.w. p.o. *Panax ginseng* did not elevate the oxidative stress in erythrocytes while slight oxidative stress was found to occur in liver.

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